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Aqueous Wittig reactions of semi-stabilized ylides. A straightforward synthesis of 1,3-dienes and 1,3,5-trienes

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ABSTRACT

A direct synthesis of 1,3-dienes and 1,3,5-trienes from the reaction of semi-stabilized ylides and a range of saturated and unsaturated aldehydes is reported in water as solvent, employing sodium hydroxide as base. The water-soluble phosphine oxide side product is removed simply by aqueous partitioning of the organic products.

1. Introduction

The development of green, environmentally benign synthetic protocols has been a subject of significant concern over the past few years both in academia and in industry.[1] In particular, solvent-free reactions and reactions in water are of increasing interest. Water is extremely inexpensive, is easy to process, and is environmentally benign.[2] Water has been generally ignored as a medium for organic reactions due to substrate solubility problems and real or perceived reagent incompatibilities. Nonetheless, organic reactions carried out in water often exhibit a rate-enhancing effect in spite of poor solubility of the substrates in water.[3,4] In addition, reactions traditionally conducted under strictly anhydrous conditions, such as the Wittig olefination, have been demonstrated to occur in aqueous media in limited cases. In this Letter we report the first examples of the aqueous Wittig reaction of trialkylallylphosphonium salt-derived semi-stabilized ylides allowing for the successful synthesis of a range of functionalized 1,3-dienes and 1,3,5-trienes in water.

The synthesis of functionalized 1,3-dienes and homologous polyenes is a central concern in synthetic organic chemistry. The 1,3-diene sub-unit is itself found in a wide range of bioactive materials including terpenoids, fatty acid-derived lipids, pheromones, and polyketides.[5] In addition, functionalized 1,3-dienes are of central importance as the 4π-component in Diels–Alder cycloaddition and other reactions, leading to a wide array of complex intermediates.[6] The Wittig olefination reaction of a triphenylallylidenyl ylide with a carbonyl compound, conducted under anhydrous conditions, is possibly the most general method available for preparing functionalized 1,3-dienes, Figure 1.[7a–c] While the use of triphenylphosphine-derived ylides (R′ = Ph) generally results in poor (*E*):(*Z*) stereoselection, subsequent methods advanced by Vedejs,[7d] Tamura,[7d,e] Schlosser,[7f] and others[7g] using mixed aryl/alkyl and alkyl-substituted phosphines were shown to provide higher levels of (*E*)-olefin stereoselectivity. Other recent related methods for the synthesis of conjugated alkenes include the use of ylides derived from arsonium salts,[7h] in addition to a variety of metal-catalyzed cross-coupling processes.[7i]

We recently reported the first examples of the Wittig reaction involving trialkylphosphine-derived semi-stabilized benzylidenyl ylides in water.[8] Water has been used previously as the reaction medium for the Wittig reaction of stabilized ylides[9] giving unsaturated esters. The reaction of triphenyl-substituted benzylidenyl ylides with aldehydes has also been reported in water,[10] providing stilbenes with poor configurational selectivity and requiring chromatographic purification to remove triphenylphosphine oxide. To our knowledge, the use of trialkyl allylidenyl ylides has not heretofore been performed in aqueous media. In our recent report,[8] triethylbenzyl phosphonium salts were converted chemoselectively to the benzylidenyl phosphorane in water using simply sodium or lithium hydroxide as base. These ylides were shown to react with a range of aldehydes yielding stilbenes and 1-phenylalkenes in high yield. The major advantages of this process are the high (*E*)-olefin stereoselectivity and the easy separation of the water-soluble triethylphosphine oxide from the organic product which generally precipitated from the aqueous solution.

2. Results and discussion

We first investigated the aqueous Wittig reaction of ylides derived from the three different trialkylallyl-phosphonium salts shown in Figure 1. These salts were pre-formed by the reaction of the corresponding tertiary phosphine with allyl bromide.[12] The salts were dissolved in aqueous sodium hydroxide (4 equiv) and 3,4,5-trimethoxybenzaldehyde was added. The reaction went to completion within one hour at 70 °C yielding the desired 1-phenyl-1,3-diene. Both the isolated chemical yield and the

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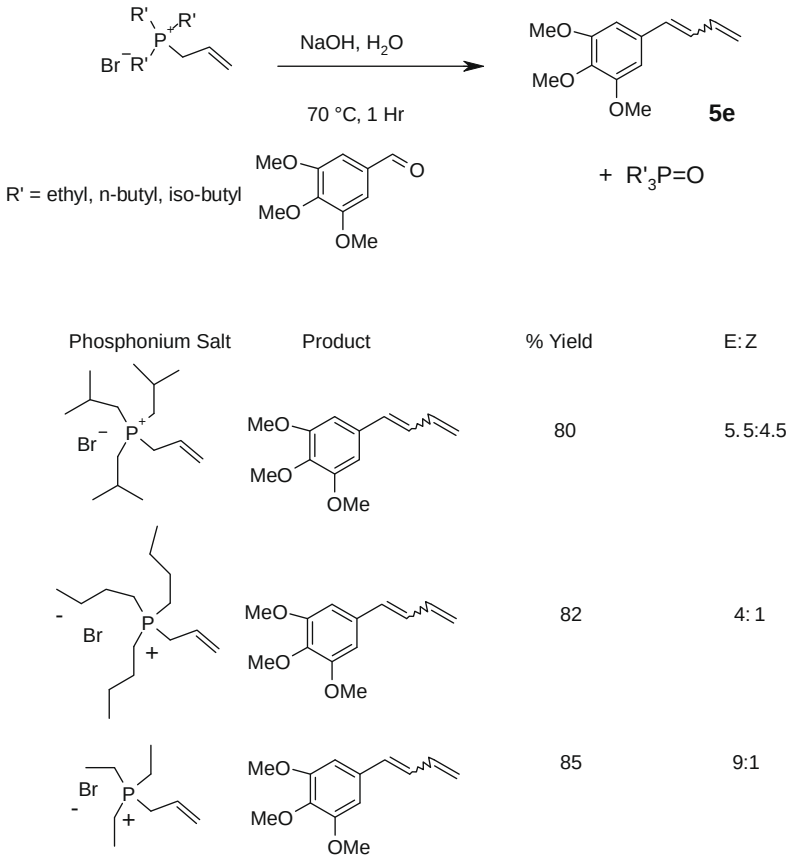


Figure 1. Screening the Wittig reaction of various trialkylallyl phosphonium salts using sodium hydroxide in water.

(*E*)-stereoselectivity of the resulting diene were shown to be highest for the triethylallyl-derived ylide. The triethylallylphosphonium bromide was next screened in the aqueous Wittig reaction with a range of aromatic aldehydes, solely in aqueous sodium hydroxide under the conditions described above. The overall results of this investigation are summarized in Table 1.

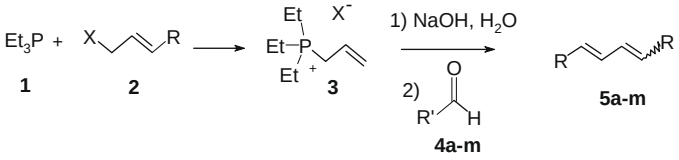
In many cases, the product diene oils-out or precipitates from the aqueous media during the reaction or upon cooling. The dienes were partitioned between dichloromethane and water and ran through a short column of silica to effect isolation of the (*E*):(*Z*) mixture. In a few cases the individual stereoisomers were readily separable. The isolated yields of the 1,3-dienes were high in all cases investigated. The (*E*):(*Z*)-stereoselectivity of the aqueous Wittig reaction was also generally high, and in accord with earlier results conducted in THF using *t*-BuOK or *n*-BuLi as base.[7c,e] The reaction of the triethylallylidenyl ylide with benzaldehyde was also carried out at room temperature, giving the 1,3-diene with 70% conversion after 3 h. Analysis of this crude product showed the formation of the dienes in the same 4:1 (*E*):(*Z*) ratio as reported in Table 1, indicating that the configurational selectivity observed is not subject to any significant thermodynamic isomerization under the reactions conditions or subsequent silica gel chromatography. The general reaction proved applicable to a wide range of hetero-substituted aromatic aldehydes, including *ortho*-substituted derivatives. The reactions of both 2-chloro benzaldehyde and 2-fluoro benzaldehyde resulted in higher (*Z*)-stereoselectivity than initially anticipated. The increased (*Z*)-stereoselectivity and anamolous effects of 2-halo benzaldehyde derivatives have been reported previously.[11]

The aqueous Wittig reaction of ylides derived from triethylallylphosphonium bromide was next investigated with a series of α,β-unsaturated and aliphatic aldehydes, the results of which are summarized in Table 2. The unsaturated aldehydes allowed ready access to the corresponding 1,3,5-trienes from a variety of skeletons including monoterpenoid, aliphatic, and aromatic cases and this appears to be very general. Isolated yields were in the 80% range with good to high (*E*) stereoselectivity being observed. Most interestingly, the enolizable aliphatic aldehydes dihydrocinnamaldehyde and dodecanal were also observed to react selectively with the allyl ylide generated under these aqueous basic conditions. Only traces of polar impurities were observed and the corresponding 1,3-dienes were isolated in 73% and 70% yields, respectively. This chemoselectivity favoring olefination over potential homo-aldol or Cannizaro-type products under conditions that are classically known to effect these reactions is startling. We have postulated that this chemoselectivity is due to the formation of phosphonium salt-stabilized micelles that effectively partition the organic materials from the aqueous basic environment during the reaction. Ylide formation occurs at the interface, and delivery of the neutral ylide and olefination take place in the organic interior of the micelle.

3. Conclusion

In conclusion, the Wittig reaction of ylides derived from trialkylallyl phosphonium salts has been demonstrated for the first time in water using sodium hydroxide as base. Ylide formation occurs exclusively through deprotonation at the allylic position. The resulting ylides were shown to react with a series of aromatic, unsaturated, and enolizable aliphatic aldehydes yielding a structurally diverse range of useful 1,3-dienes and 1,3,5-trienes. The reaction is observed to be very chemoselective for olefination

Table 1
Synthesis of 1-phenyl-1,3-dienes **5** from aromatic aldehydes **4** using the aqueous Wittig reaction[12]



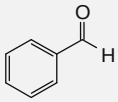
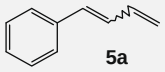
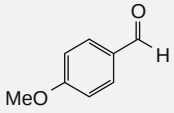
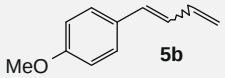
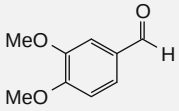
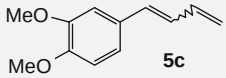
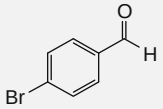
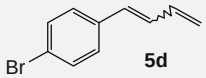
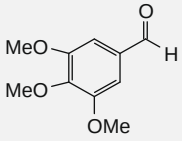
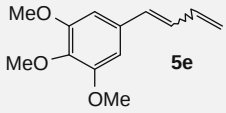
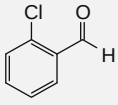
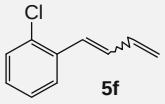
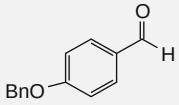
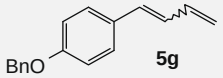
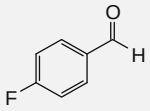
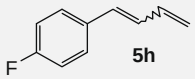
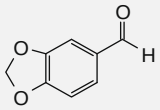
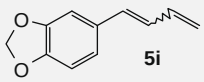
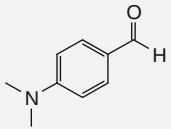
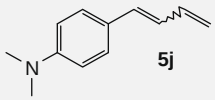
R–CHO	1,3-Diene	Yield	(*E*):(*Z*)
	 **5a**	80	4:1
	 **5b**	81	3:1
	 **5c**	85	8.5:1.5
	 **5d**	95	3:1
	 **5e**	85	9:1
	 **5f**	90	1.1:1
	 **5g**	92	4:1
	 **5h**	90	9.5:0.5
	 **5i**	85	4:1
	 **5j**	85	8.5:1.5

Table 1 (*continued*)

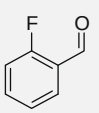
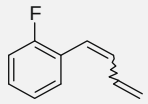
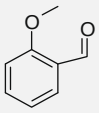
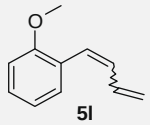
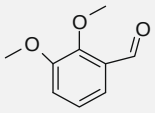
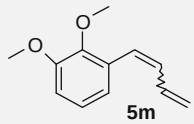
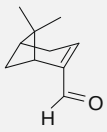
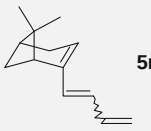
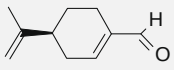
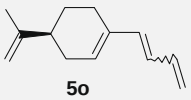
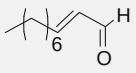
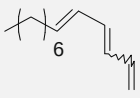
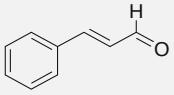
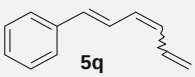
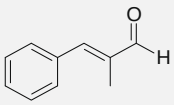
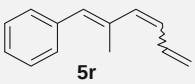
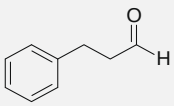
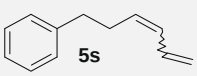
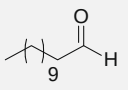
R–CHO	1,3-Diene	Yield	(*E*):(*Z*)
	 **5k**	85	7:3
	 **5l**	83	3.5:1
	 **5m**	87	4:1

Table 2
Synthesis of polyenes from trialkylallylidenyl ylides with unsaturated and enolizable aliphatic aldehydes

R–CHO	Polyene	Yield	(*E*):(*Z*)
	 **5n**	80	9:1
	 **5o**	78	9:1
	 **5p**	80	3:2
	 **5q**	80	7:3
	 **5r**	79	4:1
	 **5s**	73	4:1
	**5t**	70	4:1

under conditions where competing homo-aldol or Cannizaro disproportionation reactions might be anticipated. Further studies on the mechanism of this simple, chemoselective polyene synthesis and applications on the reactions of other trialklylphosphine-derived semi-stabilized ylides in aqueous media are under underway.

Acknowledgments

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References and notes

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12. *Representative procedure*: Synthesis of allyl-triethylphosphonium-bromide: Into a flame-dried flask was added triethylphosphine (1 mL, 6.80 mmol) in dry dichloromethane (6.8 mL) under argon at 0 °C. To this was added allyl bromide (589 μL, 6.80 mmol) via syringe. The solution was warmed to room temperature and stirred for 50 min. The solvent was evaporated under vacuum to yield the title compound in 99% yield (2.2 g) as white solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.17 (dt, J_{PH} = 19.3 Hz, J_{HH} = 7.3 Hz, 9H); 2.38 (m, 6H); 3.36 (dd, J_{PH} = 16.8 Hz, J_{HH} = 8.4 Hz, 2H); 5.2–5.8 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 6.0; 12.1 (d, J_{PC} = 48.2 Hz); 24.0 (d, J_{PC} = 46.6 Hz); 123.9 (d, J_{PC} = 12.9 Hz); 124.4 (d, J_{PC} = 11.6 Hz); ^{31}P-NMR (80 MHz, $CDCl_3$): 36.8; HRES MS $(M^+)^+$ calcd. for $C_9H_{20}P$: 159.1306, found 159.1303.*General procedure for* Tables 1 and 2: Synthesis of **5e**: Into a flame-dried flask, containing a magnetic stirring bar, was weighed allyl-triethylphosphonium bromide (238 mg, 1 mmol) and distilled water (0.4 mL) was added to make a 2.5 M solution. The contents of the flask were stirred for 15 min at room temperature whereupon powdered NaOH (160 mg, 4.0 mmol) was added slowly. After 2 min 3,4,5-trimethoxybenzaldehyde (196.2 mg, 1 mmol) was added slowly to the reaction flask. The contents of the flask were stirred vigorously at 70 °C for 1 h. The oil bath was removed and the flask was left to attain room temperature. Water (5 mL) was added to the reaction mixture and the contents of the flask were stirred for 10 min. The resulting mixture was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The product was purified over a short silica gel column (35% ethyl acetate in hexane) to yield the title compound **5e,** 186 mg, (85%) as yellow semi-solid. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 3.83 (s, 3H); 3.85 (s, 6H); 5.14 (d, J_{HH} = 10.8 Hz, 1H); 5.31 (d, J_{HH} = 17.4 Hz, 1H); 6.47 (m, 2H); 6.61 (s, 2H); 6.68 (dd, J_{HH} = 10.2 Hz, 16.2 Hz, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 56.0; 60.9; 103.4; 117.5; 129.1, 130.5; 132.8; 133.1; 137.0; 153.3; HRCI MS (M^+) calcd. for $C_{13}H_{16}O_3$: 220.1099, found: 220.1104.